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Metalated Nitriles: Electrophile-Dependent Alkylations

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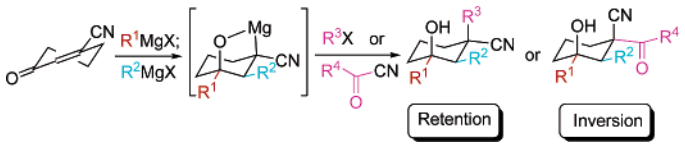
ABSTRACT



Sequential carbonyl addition–conjugate addition to oxonitriles generates a C-magnesiated nitrile exhibiting electrophile-dependent alkylation stereoselectivities. Alkylations with alkyl halides, sulfonates, and ketones proceed with retention of stereochemistry, whereas aldehyde and acyl cyanide acylations proceed with inversion of stereochemistry. BuLi-initiated conversion of the C-magnesiated nitrile to the corresponding N-lithiated nitrile reverses the alkylation stereoselectivity, providing a facile route to diastereomeric nitriles that vary at a single, quaternary stereocenter.

Chiral organometallics are extremely versatile reagents for asymmetric synthesis.[1] Historically, chiral organometallics emerged through chiral auxiliary attachment,[2] whereas complementary alkylations of chiral, sp^3-hydridized organometallics languished until α-heteroatom substitution was found to dramatically enhance configurational stability.[3] These classic studies facilitated the emergence of sparteine-mediated deprotonations[4] and access to chiral α-alkoxy- and α-aminoorganolithiums for chiral bond constructions.[5]

Several highly unusual trends have emerged from the broad use of chiral organolithiums.[6] Particularly surprising is the electrophile-dependent stereoselectivity observed with tertiary, benzylic, and allylic organolithiums. In contrast to the stereochemical retention observed in most chiral organolithium alkylations,[6] stereochemical reversals are known upon changing from carbonyl electrophiles to alkyl halides,[7] from alkyl halides to tosylates[8] or phosphates,[9] and even for alkylations in which an alkyl chloride is replaced by an alkyl bromide![10]

Electrophile-dependent alkylations of chiral organometallics bearing adjacent electron-withdrawing groups are extremely rare.[8b,11] The scarcity stems from the configurational instability induced by delocalization. Pioneering alkylations of chiral sulfoxide-stabilized organolithiums[11] identified a subtle stereoselectivity dependence on the electrophile,[11] the solvent,[12] the presence of cryptands,[12] and even the alkyllithium source![13] Not surprisingly, a complete understanding languished until more than 20 years after the original discovery.[14]

(1) *Handbook of Reagents for Organic Synthesis: Chiral Reagents for Asymmetric Synthesis*; Paquette, L. A., Ed.; Wiley: Chichester, 2003.
(2) Braun, M. In *Stereoselective Synthesis*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Houben-Weyl: New York, 1996; Vol. 2, pp 1603−1666.
(3) Still, W. C.; Sreekumar, C. *J. Am. Chem. Soc.* **1980**, *102*, 1201.
(4) (a) Hoppe, D.; Hense, T. *Angew. Chem., Int. Ed.* **1997**, *36*, 2282.
(5) (a) Gawley, R. E.; Coldham, I. In *The Chemistry of Organolithium Compounds*; Rappoport, Z., Marek, I., Eds.; Wiley: Chichester, 2004. (b) Hoppe, D.; Marr, F.; Brüggemann, T. *Top. Organomet. Chem.* **2003**, *5*, 61. (c) Beak, P.; Johnson, T. A.; Kim, D. D.; Lim, S. H. *Top. Organomet. Chem.* **2003**, *5*, 139.
(6) Clayden, J. In *Organolithiums: Selectivity for Synthesis*; Pergamon: Amsterdam, 2002; Chapter 6.
(7) Basu, A.; Thayumanavan, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 717.
(8) (a) Thayumanavan, S.; Lee, S.; Liu, C.; Beak, P. *J. Am. Chem. Soc.* **1994**, *116*, 9755. (b) Meyers, A. I.; Knaus, G. *J. Am. Chem. Soc.* **1974**, *96*, 6508.
(9) Chassaing, G.; Lett, R.; Marquet, A. *Tetrahedron Lett.* **1978**, 471.
(10) Stakemeier, H.; Würthwein, E.-U. *Liebigs Ann.* **1996**, 1833.
(11) Durst, T.; Viau, R.; McClory, M. R. *J. Am. Chem. Soc.* **1971**, *93*, 3077.
(12) Biellmann, J. F.; Vicens, J. J. *Tetrahedron Lett.* **1974**, 2915.
(13) Durst, T.; Molin, M. *Tetrahedron Lett.* **1975**, 63.
(14) Ohno, A.; Higaki, M. *Rev. Heteroatom Chem.* **1995**, *13*, 1.

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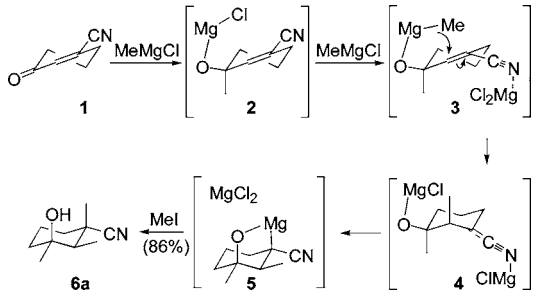
C-Magnesiated nitriles, generated by sequential 1,2−1,4-addition−conjugate addition of Grignard reagents to oxonitriles (Scheme 1),[15] exhibit a unique electrophile-dependent

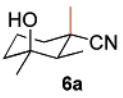
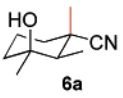
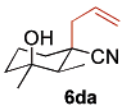
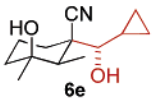
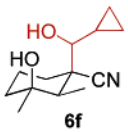
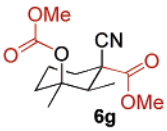
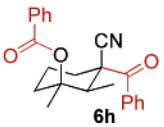
Scheme 1. Multicomponent Addition−Alkylation of Oxonitrile **1**



stereoselectivity not previously observed with N-metalated nitriles obtained by metal amide deprotonation.[16] Formation of C-magnesiated nitrile **5** is favored by internal chelation (Scheme 1, **4** → **5**), conferring a highly unusual preference for axial methylation that directly contrasts with the equatorial alkylations of conformationally locked N-metalated nitriles.[17] Surveying an array of alkylations with the C-magnesiated nitrile **5**[18] reveals an unprecedented electrophile-dependent stereoselectivity[19] and leads to a complementary stereodivergent alkylation of the corresponding N-metalated nitrile.

C-Magnesiated nitrile **5** is conveniently generated by the addition of excess MeMgCl to oxonitrile **1** (Scheme 1). Intercepting **5** with Me_2SO_4 affords the axially methylated nitrile **6a** analogous to the alkylation with MeI (Table 1, entries 1 and 2).[20] The preference for axial alkylation is maintained even with the more sterically demanding electrophiles *n*-PrI and cyclohexanone (Table 1, entries 3 and

Table 1. Electrophile-Dependent Alkylations of C-Magnesiated Nitrile **5**[a]

entry	electrophile	nitrile	yield
1	MeI	 **6a**	86%
2	Me_2SO_4	 **6a**	57%
3	*n*-PrI	 **6b**	70%
4		 **6c**	68%
5		 **6da**	71%[b]
6		 **6e**	45%
		 **6f**	11%[c]
7	MeOCOCN	 **6g**	61%
8	PhCOCN	 **6h**	55%

[a] Unequivocal stereochemical assignment is based on X-ray analysis in each case.[19] [b] Obtained as a 2:1 ratio of isomers. [c] Single unassigned stereoisomer at the carbinol stereocenter.

4), although alkylation of **5** with allyl bromide, having essentially the same steric demand as *n*-PrI, is nonselective (2:1 ratio, Table 1, entry 5).[21] The retentive alkylations with alkyl halide, sulfonate, and ketone electrophiles are starkly contrasted by the equatorial acylations of cyclopropanecarboxaldehyde, methyl cyanoformate, and benzoyl cyanide (Table 1, entries 6−8),[22] with the latter two equatorial

(15) Fleming, F. F.; Zhang, Z.; Wang, Q.; Steward, O. W. *Angew. Chem., Int. Ed.* **2004**, *43*, 1126.

(16) (a) Fleming, F. F.; Shook, B. C. *Tetrahedron* **2002**, *58*, 1. (b) Arseniyadis, S.; Kyler, K. S.; Watt, D. S. *Org. React.* **1984**, *31*, 1.

(17) Bare, T. H.; Hershey, N. D.; House, H. O.; Swain, C. G. *J. Org. Chem.* **1972**, *37*, 997.

(18) Although unusual, C-metalated nitriles are known for Li, Mg, and Zn: (a) Boche, G.; Harms, K.; Marsch, M. *J. Am. Chem. Soc.* **1988**, *110*, 6925. (b) Thibonnet, J.; Vu, V. A.; Berillon, L.; Knochel, P. *Tetrahedron* **2002**, *58*, 4787. (c) Goasdoue, N.; Gaudemar, M. *J. Organomet. Chem.* **1972**, *39*, 17. For alkylations of chiral Grignard reagents, see: Hoffmann, R. W. *Chem. Soc. Rev.* **2003**, *32*, 225.

(19) Stereochemical assignments are based on X-ray analysis for **6a**−**e**,**g**,**h**, with the crystallographic data being deposited with the Cambridge Crystallographic Data Center (CCDC 218678, 242090, 242091, 242092, 242093, 24209, and 242095, respectively). The supplementary crystallographic data can be obtained free of charge via the Internet at www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, UK (fax +44 1223 336033; or e-mail deposit@ccdc.cam.ac.uk).

(20) **General Procedure.** A THF solution of MeMgCl (3.5 equiv) was added to a −78 °C, THF solution (0.1 M) of the oxonitrile **1**, and the mixture was stirred at −78 °C for 1 h and then warmed to room temperature. After 1.5 h, the electrophile (3 equiv) was added neat either at room temperature or with prior cooling to −78 °C. Subsequent addition of saturated NH_4Cl and extraction with EtOAc afforded a crude product that was washed with brine and dried ($MgSO_4$), concentrated, and purified by radial chromatography to afford the pure nitrile.

(21) Loss of stereocontrol with allyl bromide does not seem to arise from a mechanistic changeover to a single electron-transfer reaction since preliminary alkylations with cyclopropylmethyl iodide proceed without ring opening: Gawley, R. E.; Low, E.; Zhang, Q.; Harris, R. *J. Am. Chem. Soc.* **2000**, *122*, 3344.

(22) For an analogous equatorial alkylation of a related C-magnesiated nitrile with benzaldehyde, see: Fleming, F. F.; Wang, Q.; Steward, O. W. *J. Org. Chem.* **2003**, *68*, 4235.

acylations installing four new bonds and three stereocenters in one synthetic operation.

The electrophile-dependent alkylations of **5** are consistent with the excellent stereoelectronic rationale[23] advanced for S_E2[24] alkylations of chiral organolithiums. Alkyl halides and sulfonates, as well as large ketones, alkylate with retention of configuration through a side-on overlap of σ^* or of π^* for cyclohexanone, with the large lobe of the metal carbon σ-bond (Figure 1, **5a′**) since the collinear trajectory (**5a″**) is

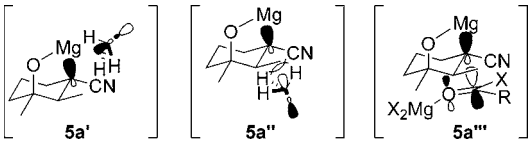


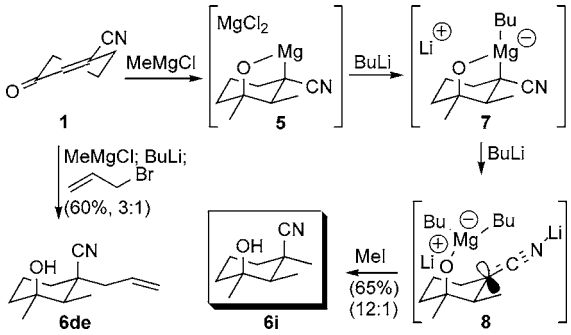
Figure 1. Stereoelectronically controlled alkylations.

sterically prohibited. Small magnesium dihalide-complexed carbonyl electrophiles with large, diffuse, low-lying LUMOs preferentially react with the small lobe of the carbon−metal σ-bond (Figure 1, **5a‴**).

The stereoelectronically controlled alkylation of the C-magnesiated nitrile **5** stimulated a stereodivergent alkylation that highlights the stark reactivity differences of the corresponding N-metalated nitrile. Addition of excess BuLi to **5** (Scheme 2) triggers conversion to the putative N-metalated nitrile **8**, which upon methylation with MeI, predominantly affords the diastereomeric nitrile **6i**. The stereoselectivity is consistent with initial conversion of **5** to the bicyclic ate **7** and, with excess BuLi, conversion to the magnesium ate **8**,[25] where equatorial alkylation occurs from the more accessible face.[26] An analogous stereochemical reversal occurs during the allylation leading to **6de**, although the more reactive allyl bromide is less selective for equatorial alkylation than MeI

(23) Carstens, A.; Hoppe, D. *Tetrahedron* **1994**, *50*, 6097.
(24) For an excellent overview of terms and orbital overlap, see: Gawley, R. E. *Tetrahedron Lett.* **1999**, *40*, 4297.
(25) Inoue, A.; Kitagawa, K.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **2001**, *66*, 4333.
(26) Fleming, F. F.; Zhang, Z. *Tetrahedron* **2005**, *61*, 747.

Scheme 2. Stereodivergent Alkylations of N-Metalated Nitriles



(Scheme 2). Collectively, the 1,2−1,4-Grignard additions, with and without BuLi, provide facile access to diastereomeric nitriles that vary at a single quaternary center.

C-Magnesiated nitriles exhibit electrophile-dependent stereoselective alkylations not previously observed with N-metalated nitriles. Alkylation with alkyl halide, sulfonate, and ketone electrophiles proceed with retention of stereochemistry, whereas aldehyde and acyl halide acylations proceed with inversion of stereochemistry, consistent with the stereoelectronic model proposed for reactions of chiral organometallics. Conversion of the C-metalated nitrile to the corresponding N-metalated nitrile permits stereodivergent alkylations, providing, for the first time, diastereomeric, quaternary nitriles from a single precursor. Collectively, the electrophile-dependent alkylations demonstrate the potential for stereoselective alkylations of C-metalated nitriles and their complementary reactivity with the typical N-metalated nitrile counterparts.

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Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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